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ORIGINAL RESEARCH

Comparison of the Efficacy of 2 Different Botulinum Toxin Injection Techniques in Gastrocnemius Muscle Spasticity in Hemiplegic Patients: A Randomized Double-Blind Controlled Study

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Abstract

Objective: To compare the efficacy of the innervation zone–targeted injection technique (EUROMUSCULUS/USPRM (Ultrasound Study Group of the International Society of Physical and Rehabilitation Medicine) spasticity approach) and the injection technique along the muscle length.

Design: A double-blind randomized controlled trial.

Setting: Department of rehabilitation medicine of a medical center.

Participants: One hundred patients with stroke experiencing ankle plantar flexor spasticity.

Interventions: In addition to conventional rehabilitation, eligible patients were randomly assigned to 2 groups. The experimental group was injected with botulinum toxin along the length of the muscle, whereas the control group was injected with the same dose and volume of botulinum toxin 25%-35% proximal to the medial head and 20%-30% proximal to the lateral aspect of the head of the gastrocnemius muscle.

Main Outcome Measures: Modified Ashworth scale, modified Tardieu scale, ankle range of motion measurement, and 10-meter walk test were used before and 1 month after injection.

Results: The study was completed by 60 participants with a mean age of 59.96±12.15 years. Both injection methods were found to be effective on range of motion, spasticity level, ambulation, and walking speed. There was no statistically significant difference between injection methods.

Conclusions: Both injection methods of botulinum toxin A produce similar clinical effects.

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Numerous types of neurologic disorders, including stroke, multiple sclerosis, hypoxic brain injury, traumatic brain injury, spinal cord injury, tumors, and degenerative diseases, may occur with spasticity as a clinical symptom. Spasticity was defined as "a motor disorder characterized by a rate-dependent increase in the muscle stretch reflex, also called myotatic, accompanied by hyperreflexia and hypertonia due to neural hyperexcitability, with exaggerated movements in the tendons, which is indicative of signs of upper motor neuron syndrome."[1] In stroke, it is estimated that about 38%-40% of patients will have some degree of spasticity and 16% will need treatment.[2,3] This will be different depending on the time elapsed, ranging from 27% per month to 42.6% in the chronic phase.[4] Spasticity may have beneficial effects, such as preventing bone decalcification, providing muscle tone for standing, providing cardiovascular benefits, and reducing the likelihood of deep vein thrombosis, but it may also have effects that require treatment, such as contractures, pain, abnormal postures (dystonia), restricted mobility, and increased risk of pressure ulcers.[5,6] In the treatment of spasticity, nonpharmacologic patient and caregiver education, stretching, splint/breys, sometimes serial casts, physical therapy modalities (ultrasound, thermotherapy, extracorporeal shock wave therapy), strengthening exercises, neuromuscular electrical stimulation, pharmacologic oral antispastic agents, local phenol/alcohol and botulinum toxin (BoNT) injections and surgical treatments are used.[7]

BoNT blocks the release of acetylcholine from motor terminals and therefore action potentials reaching the motor end plate cannot

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cause contraction in the muscle.[8] It has been reported that applying the injection to the area where the motor endplates are dense increases the efficacy.[9] In the cadaveric study, it was demonstrated that the motor points of the gastrocnemius and soleus muscles were located along the length of the muscle.[10] In the light of this information, injection of BoNT along the length of the muscle (along the motor endplates localization) may be more effective.

The aim of this study was to compare the efficacy of the innervation zone−targeted injection technique (EUROMUSCULUS/USPRM (Ultrasound Study Group of the International Society of Physical and Rehabilitation Medicine) spasticity approach) and the motor endplate-targeted technique (injection along the muscle length).

Methods

The study was designed as a randomized double-blind controlled trial. Approval for the study was obtained from Necmettin Erbakan University Meram Faculty of Medicine Clinical Research Ethics Committee and the Turkish Ministry of Health Pharmaceuticals and Medical Devices Agency. Informed consent form was obtained from the participants.

Participants

The study included 100 outpatients and inpatients between November 2022 and January 2024 who were scheduled for BoNT injection because of spasticity affecting ankle movements. Participants who were >18 years of age, who were scheduled for BoNT injection because of spasticity in the gastrocnemius muscle and who were willing to participate in the study were included in the study. Those with spasticity in other muscles affecting ankle movements, those using myorelaxant or myospasm-inducing drugs, those who had BoNT treatment within the last 3 months, and those with ankle and knee contractures due to orthopedic reasons were excluded. The participants were divided into 2 equal groups by block randomization method. Participants were divided into 10 blocks. The group of the first participant in the blocks was determined by coin toss method and then arranged consecutively as the other group (Experimental group - control group). Randomization was performed by H.Y.

Evaluation parameters

Participants were evaluated with modified Ashworth scale, modified Tardieu scale, ankle range of motion measurement, and 10-meter walk test (10MWT) before injection and at the first month after administration when BoNT reached maximum effect. Assessments were performed by the same investigator blinded to the treatment modality.

The modified Ashworth scale is a 6-level scale commonly used for the assessment of spasticity.[11]

10MWT

Short-distance ground walking speed and ability were assessed using the 10MWT. Participants were informed about the test. Participants walked at a comfortable pace on a 10-meter walkway and were timed. Participants were allowed to use walking aids and/or ankle-foot orthosis during the test.[12]

Modified Tardieu scale

The evaluator first moved the joint as slowly as possible (V1) through the total range of motion. The angle was measured with a universal goniometer by another physicist who placed the goniometer close to the joints and read the values. The full range of motion was defined as R2. The evaluator then moved the joint as fast as possible (V3) in the same direction and in the same full arc of motion. The angle of the muscle reaction (a clear catch or clonus) was measured with a goniometer and recorded as R1. The difference between R2 and R1 (R2-R1) reflects the dynamic tone component of spasticity. The greater the spasticity angle, the more spastic the muscle.[13]

Interventions

In the control group, ultrasonography-guided injection was performed between 25% and 35% proximal to the medial head and 20%-30% proximal to the lateral aspect of the head of the gastrocnemius muscle.[14] The experimental group was injected along the length of the muscle under ultrasonography guidance (fig 1). The same dose and volume (200 IU onabotulinum toxin A, 4 mL) was used in both groups. All injections were administered by the same investigator blinded to the treatment group. All participants received individual rehabilitation for 1 hour a day, 5 days a week for 1 month. No specific rehabilitation protocol was established for the study. Individual rehabilitation was applied for their disabilities.

No side effects were observed.

In the power analysis based on the modified Ashworth scale value, it was calculated that the groups should consist of 23 participants each for the study to have 80% power.[15]

Statistical analysis

SPSS version 26.0[a] was used for statistical analysis of the data collected. The Shapiro-Wilk test was used for the normality test. Normally distributed measurement data are presented as mean ± SD and nonnormally distributed data are presented as median (minimum to maximum). In intergroup comparisons, independent samples *t* test was used for normally distributed data and Mann-Whitney *U* test was used for nonnormally distributed data. In intragroup comparisons, paired samples *t* test was used for data fitting the normal distribution and Wilcoxon signed-rank test was used for data not fitting the normal distribution. For statistical significance, $P<.05$ was accepted.

Results

The study was completed by 60 participants (16 women, 44 men) with a mean age of 59.96±12.15 years. Seventeen participants from the control group and 16 participants from the experimental group were excluded from the study because of spasticity in ≥1 other muscle groups affecting the ankle, and 3 participants from the control group, and 4 participants from the experimental group were excluded from the study because they did not follow-up (fig 2). There were no significant demographic differences between the groups (table 1).

Both injection methods were found to be effective on range of motion, spasticity level, ambulation, and walking speed.

List of abbreviations:

10MWT	**10-meter walk test**
BoNT	**Botulinum neurotoxin**
BoNT-A	**Botulinum neurotoxin type A**
HD-sEMG	**high-density surface electromyography**

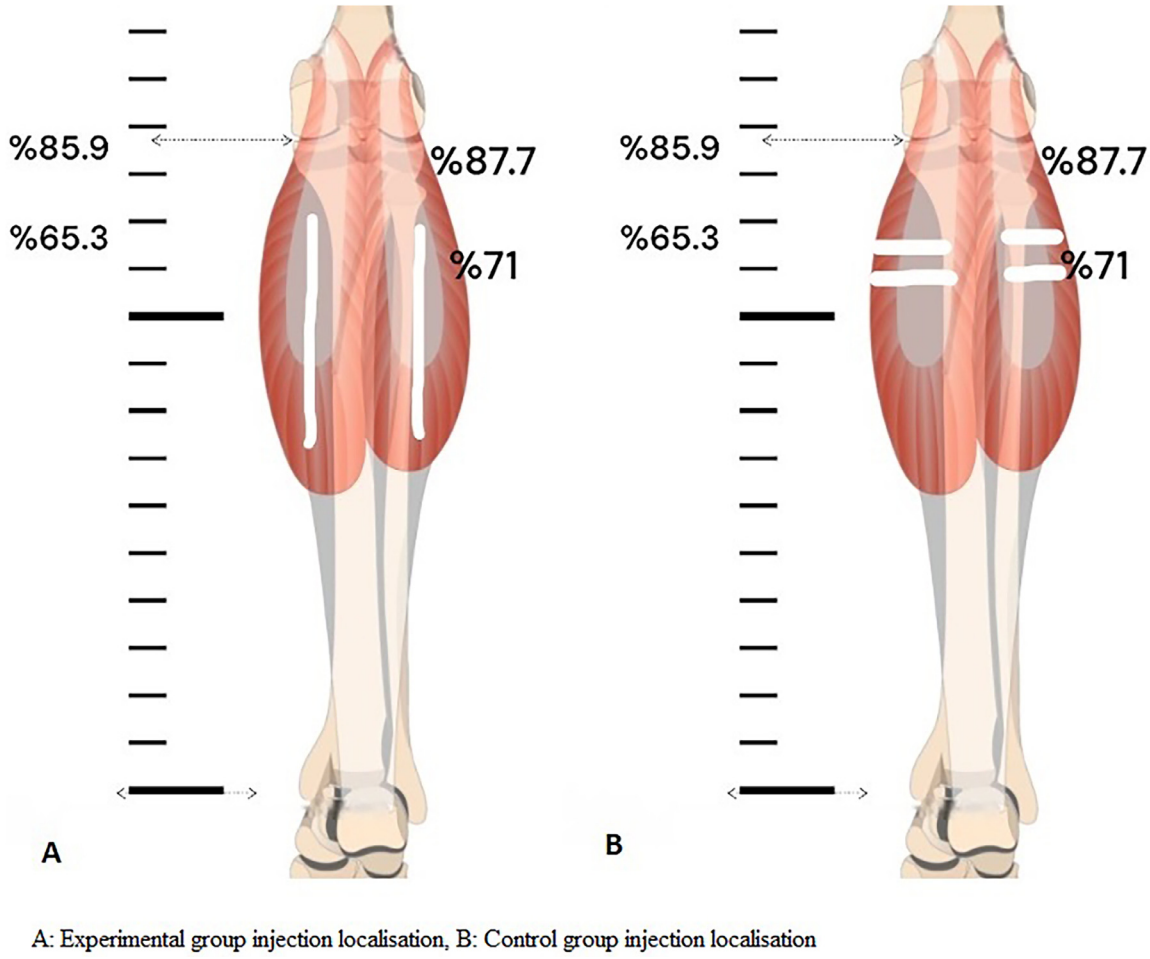

Fig 1 Injection localization.

There was no statistically significant difference between injection methods (table 2).

Discussion

In this study in which we compared the efficacy of 2 different methods of BoNT administration in the treatment of spasticity in the gastrocnemius muscle after stroke, it was demonstrated that both methods were effective on range of motion, spasticity level, ambulation level, and walking speed. It was also demonstrated that there was no significant difference in efficacy between these 2 injection methods.

BoNT type A (BoNT-A) is the first-line pharmacologic therapy for the treatment of poststoke focal and multifocal spasticity and should be part of a rehabilitation program to promote clinical efficacy.[16,17] Although BoNT-A is an established treatment for focal spasticity, there is little consensus on how to maximize efficacy. Research has focused on individualized approach, injection technique (storage, dilution, analgesia, injection guidance, conversion ratio) and adjunctive treatment.[18] Although end plate and innervation zone targeting makes theoretical sense, few studies have so far demonstrated its clinical relevance.

High-volume or endplate-targeted BonNT-A injections have been reported to provide greater spasticity reduction in biceps spasticity and improvement in active elbow extension range than low-volume, nontargeted injections.[19] In the trapezius muscle, which is a thinner muscle, it has been determined that the application of BoNT-A with intramuscular nerve branching technique for aesthetic purposes provides more thinning compared with conventional application.[20] In elbow flexor spasticity, the same dose and volume of BoNT-A administered by motor point targeting and intramuscular distribution were found to be similarly effective.[15] It was observed that injection of the same volume and dose of BoNT-A into the medial 2/10-3/10 of the gastrocnemius muscle and into the muscle belly had similar electromyographic and clinical effects.[21] We found that BoNT-A applications at the same dose and volume by spreading along the length of the medial and lateral aspect of the head with 4-point application to the medial head 25% and 35%, lateral aspect of the head 20% and 30% of the gastrocnemius muscle under ultrasonography guidance had similar effects after 1 month. In the study conducted with high-density surface electromyography (HD-sEMG), increasing the injection distance from the endplate area by 1 cm reduced the effect of BoNT-A by 46%.[22] It enhances the efficacy of BoNT in managing spasticity using the 3-dimensional innervation zone imaging technique based on HD-sEMG recordings.[23] In the study in which we targeted the topographic location of the innervation zone under Ultrasonography (USG) guidance, no similar difference in effect was detected.

Although targeting the motor endplate is theoretically thought to increase the effect considering the BoNT-A mechanism of

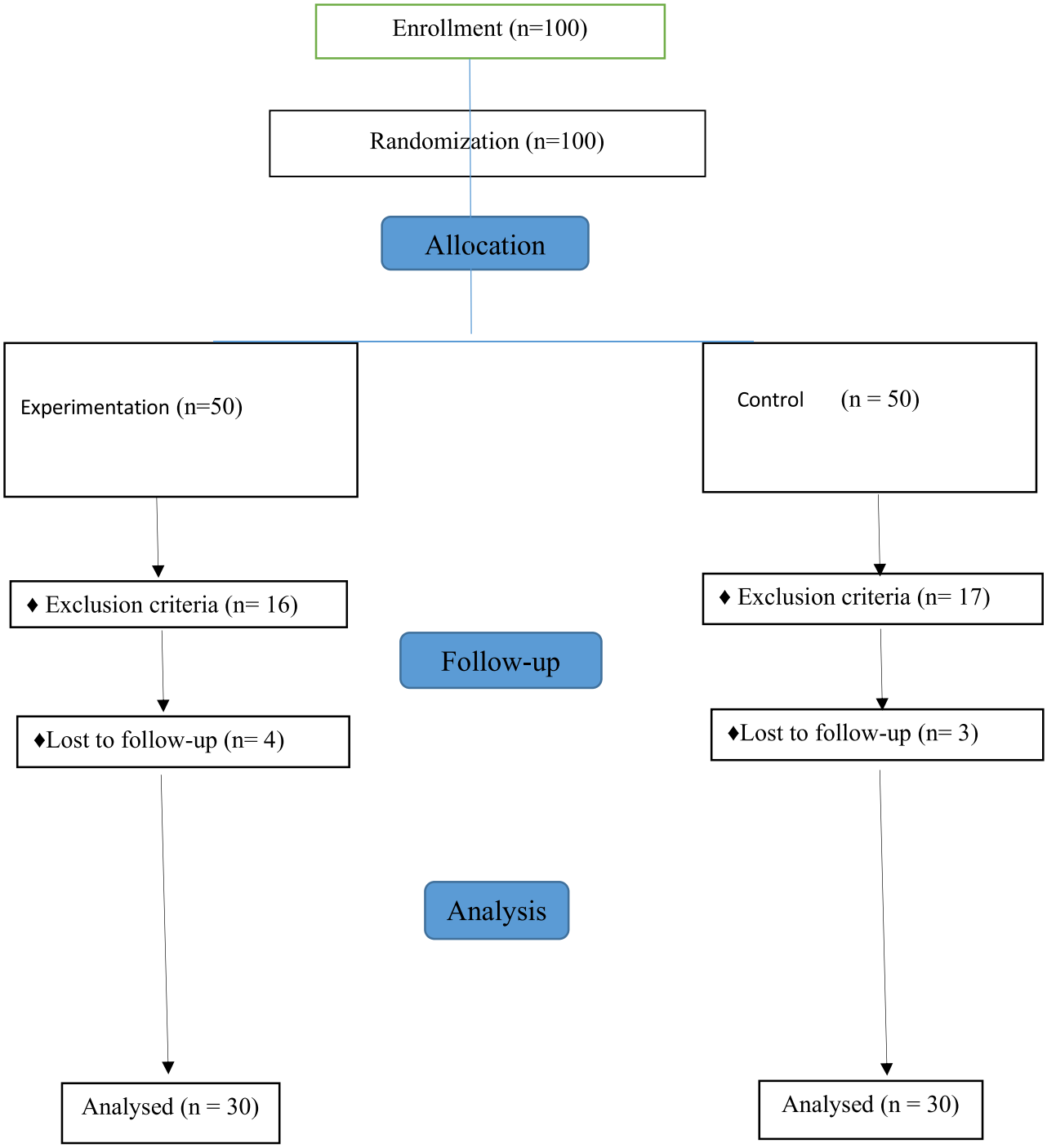

Fig 2 CONSORT flow diagram of the study.

Table 1 Demographic characteristics of the participants.

Characteristic	Experimentation (n=30)	Control (n=30)	*P*
Age (y), mean ± SD	61.63 ± 10.66	58.3 ± 13.45	.292*
BMI (kg/m^2), mean ± SD	27.58 ± 5.01	27.27 ± 3.07	.774*
Female sex (%)	23.33	30	.771*
Duration of disease (mo)	12 (3 132)	16 (4 72)	.683†

Abbreviation: BMI, body mass index.
* Independent samples *t* test.
† Mann-Whitney *U* test.

action, it has not yet been supported by studies. This contradiction between theoretical knowledge and clinical practice may be attributed to the fact that both injection methods are inadequate to reach the endplates, BoNT-A has a similar effect on the endplates in both methods with its 5 cm spread potential, and BoNT-A produces functional results with its retrograde long-distance effects in the central nervous system.[24,25]

Our study showed that BoNT-A injection along the length of the muscle produced similar effects in parallel with the studies showing that BoNT-A applied at different points produced similar effects in gastrocnemius spasticity.[26,27] Given that the location of

Table 2 In-group and intergroup comparisons.

Variable	Experimentation (n=30)	Control (n=30)	Between-Group Analysis (*P*)
ROM			
T0	46.3±11.31	46.6±11.36	
T1	56.63±7.3	55.86±10.58	
t	−9.14	−5.22	
*P**	**<.001**	**<.001**	
T0-T1	1.8±1.42	−2.26±1.41	.348†
MAS			
T0	2.6±0.62	2.5±0.68	
T1	1.53±0.68	1.6±0.72	
t	8.44	7.44	
*P**	**<.001**	**<.001**	
T0-T1	1.06±0.69	−0.9±0.66	.344†
MTS			
T0	2.56±0.72	2.46±0.89	
T1	1.6±0.72	1.66±0.84	
t	7.37	6.13	
*P**	**<.001**	**<.001**	
T0-T1	0.96±0.71	0.8±0.71	.371†
Delta			
T0	9.73±4.96	12.23±6.31	
T1	5.76±3.32	6.96±3.38	
t	5.93	5.38	
*P**	**<.001**	**<.001**	
T0-T1	3.66±3.66	−5.26±5.35	.277†
FAS			
T0	3.73±1.43	3.53±1.3	
T1	4.26±1.25	3.93±1.33	
t	−4.64	−4.39	
*P**	**<.001**	**<.001**	
T0-T1	−0.53±0.62	−0.4±0.49	.366†
10MWT			
T0	37.07 (9.14-120)	41.65 (10.77-146)	
T1	30.27 (8.63-106)	37.11 (9.1-149)	
t	−4.26	−3.79	
P‡	**<.001**	**<.001**	
T0-T1	−1.36±2.8	−1.5±3.7	.819†

Abbreviations: 10MWT, 10-meter walk test; Delta, dynamic tone component of spasticity; FAS, functional ambulation scale; MAS, modified Ashworth scale; MTS, modified Tardieu scale; ROM, range of motion.
Statistically significant values are indicated in bold.
* Paired samples *t* test.
† Independent samples *t* test.
‡ Wilcoxon signed-rank test.

the application does not change the effectiveness, it may be more effective to direct the studies to issues such as dose and concentration in order to increase the effectiveness.

Study limitations

The results of the study should be interpreted with some limitations in mind. Most importantly, HD-sEMG was not used to determine the end plate and innervation zone. The lack of electromyographic methods in the evaluation of spasticity is also a limitation. An important element of the study is the first use of the muscle length injection method, which targets the distribution of nerve endings along the muscle length, which has been demonstrated in cadaveric studies.

Conclusions

In poststroke gastrocnemius spasticity, injection of BoNT along the length of the muscle and the innervation zone−targeted injection technique produces similar clinical effects.

Suppliers

a. SPSS, version 26.0; IBM Corp.

Keywords

Botulinum toxin; Hemiplegia; Injection technique; Rehabilitation; Spasticity

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References

1. Lance JW. What is spasticity? Lancet 1990;335:606.
2. Miyara K, Kawamura K, Matsumoto S, et al. Acute changes in cortical activation during active ankle movement after whole-body vibration for spasticity in hemiplegic legs of stroke patients: a functional near-infrared spectroscopy study. Top Stroke Rehabil 2020;27:67–74.
3. Jin Y, Zhao Y. Post-stroke upper limb spasticity incidence for different cerebral infarction site. Open Med (Wars) 2018;13:227–31.
4. Wissel J, Manack A, Brainin M. Toward an epidemiology of post-stroke spasticity. Neurology 2013;80(Suppl 2):S13–9.
5. Bhimani R, Anderson L. Clinical understanding of spasticity: implications for practice. Rehabil Res Pract 2014;2014:279175.
6. Nair KP, Marsden J. The management of spasticity in adults. BMJ 2014;349:g4737.
7. Bethoux F. Spasticity management after stroke. Phys Med Rehabil Clin N Am 2015;26:625–39.
8. Kao I, Drachman DB, Price DL. Botulinum toxin: mechanism of presynaptic blockade. Science 1976;193:1256–8.
9. Childers MK, Kornegay JN, Aoki R, Otaviani L, Bogan DJ, Petroski G. Evaluating motor end-plate-targeted injections of botulinum toxin type A in a canine model. Muscle Nerve 1998;21:653–5.
10. Kim MW, Kim JH, Yang YJ, Ko YJ. Anatomic localization of motor points in gastrocnemius and soleus muscles. Am J Phys Med Rehabil 2005;84:680–3.
11. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther 1987;67:206–7.
12. Chang KW, Lin CM, Yen CW, Yang CC, Tanaka T, Guo LY. The effect of walking backward on a treadmill on balance, speed of walking and cardiopulmonary fitness for patients with chronic stroke: a pilot study. Int J Environ Res Public Health 2021;18:2376.
13. Banky M, Williams G, Davey R, Tirosh O. Inertia sensors for measuring spasticity of the ankle plantarflexors using the modified Tardieu scale—a proof of concept study. Sensors (Basel) 2022;22:5151.
14. Kaymak B, Kara M, Tok F, et al. Sonographic guide for botulinum toxin injections of the lower limb: EUROMUSCULUS/USPRM spasticity approach. Eur J Phys Rehabil Med 2018;54:486–98.
15. Mayer NH, Whyte J, Wannstedt G, Ellis CA. Comparative impact of 2 botulinum toxin injection techniques for elbow flexor hypertonia. Arch Phys Med Rehabil 2008;89:982–7.

16. Teasell R, Foley N, Pereira S, Sequeira K, Miller T. Evidence to practice: botulinum toxin in the treatment of spasticity post stroke. Top Stroke Rehabil 2012;19:115–21.
17. Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2016;86:1818–26.
18. Francisco GE, Balbert A, Bavikatte G, et al. A practical guide to optimizing the benefits of post-stroke spasticity interventions with botulinum toxin A: an international group consensus. J Rehabil Med 2021;53. jrm00134.
19. Gracies JM, Lugassy M, Weisz DJ, Vecchio M, Flanagan S, Simpson DM. Botulinum toxin dilution and endplate targeting in spasticity: a double-blind controlled study. Arch Phys Med Rehabil 2009;90. 9-16.e2.
20. Wang L, Zhang M, Li T, et al. Nerve distribution method is superior to the conventional method in BoNT-A treatment of trapezius hypertrophy: a randomized controlled trial. Aesthetic Plast Surg 2024;48: 1210–7.
21. Im S, Park JH, Son SK, Shin JE, Cho SH, Park GY. Does botulinum toxin injection site determine outcome in post-stroke plantarflexion spasticity? Comparison study of two injection sites in the gastrocnemius muscle: a randomized double-blind controlled trial. Clin Rehabil 2014;28:604–13.
22. Lapatki BG, van Dijk JP, van de Warrenburg BP, Zwarts MJ. Botulinum toxin has an increased effect when targeted toward the muscle's endplate zone: a high-density surface EMG guided study. Clin Neurophysiol 2011;122:1611–6.
23. Zhang C, Chen YT, Liu Y, et al. Improving botulinum toxin efficiency in treating post-stroke spasticity using 3d innervation zone imaging. Int J Neural Syst 2021;31:2150007.
24. Borodic GE, Pearce LB, Smith K, Joseph M. Botulinum a toxin for spasmodic torticollis: multiple vs single injection points per muscle. Head Neck 1992;14:33–7.
25. Antonucci F, Rossi C, Gianfranceschi L, Rossetto O, Caleo M. Long-distance retrograde effects of botulinum neurotoxin A. J Neurosci 2008;28:3689–96.
26. Childers MK, Stacy M, Cooke DL, Stonnington HH. Comparison of two injection techniques using botulinum toxin in spastic hemiplegia. Am J Phys Med Rehabil 1996;75:462–9.
27. Sätilä H, Pietikäinen T, Iisalo T, et al. Botulinum toxin type A injections into the calf muscles for treatment of spastic equinus in cerebral palsy: a randomized trial comparing single and multiple injection sites. Am J Phys Med Rehabil 2008;87:386–94.